PRECLINICAL TOXICITY OF 1α-HYDROXYVITAMIN D5 IN RATS AND DOGS

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1α-Hydroxyvitamin D5 [24-ethylcholecalciferol; 1α(OH)D5] is a new vitamin D analog being developed for chemoprevention and therapy of breast cancer. We have previously demonstrated that 1α(OH)D5 induces differentiation and growth inhibition in number of breast cancer cell lines. When administered to rats as a dietary supplement [50μg/kg diet], 1α(OH)D5 reduces the incidence and number of carcinogen-induced mammary carcinomas; chemopreventive activity was achieved without increases in serum calcium or phosphate levels. The present studies were performed to characterize the toxicity of subchronic administration of 1α(OH)D5. CD rats [10/sex/group] and beagle dogs [3/sex/group] received daily oral (gavage) administration of 1α(OH)D5 for four weeks. A complete battery of in-life, clinical pathology, and histopathology evaluations was performed in both studies. In rats, administration of 1α(OH)D5 at doses ranging from 2.5 to 10 μg/kg body weight/day induced no mortality or clinical evidence of toxicity; body weights in treated groups were comparable to those of corn oil controls. Serum calcium demonstrated small, but dose-related and statistically significant increases [11.0 + 0.46 mg/dL in controls versus 11.6 + 0.73 mg/dL in the high dose group]; this was not accompanied by renal toxicity and was reversed in recovery animals observed for 2 weeks after cessation of dosing. In dogs, administration of 1α(OH)D5 at 5μ/kg/day induced no clinical evidence of toxicity; doses of 10 μg/kg or above resulted in body weight loss and/or gross toxicity. Dose-related elevations in serum calcium were seen at all dose levels in dogs. These data suggest that the maximum tolerated dose [MTD] for 1α(OH)D5 is > 10 μg/kg/day in rats and 5μg/kg/day in dogs. When considered with published data, these results suggest that the MTD for 1α(OH)D5 in both rats and dogs is higher than is the MTD for its active metabolite, 1α,25 dihydroxyvitamin D3. (Supported by DAMD 17-99-1-9223 and R01-82316)

EXHIBIT C